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Effectiveness of First-Line Empirical Treatment in Portugal: Data from the European Registry on *Helicobacter pylori* Management

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Keywords

Helicobacter pylori · Endoscopy · Eradication · Empirical treatment

Abstract

Introduction: As Portugal exhibits some of the highest gastric cancer rates in Europe, optimizing the *Helicobacter pylori* eradication rate is imperative. We aimed to describe *H. pylori* treatment regimens in Portugal, within a real clinical practice setting. ***Methods:*** This is a prospective cohort study of the Portuguese patients diagnosed with *H. pylori* between May 2013 and December 2022, within the European Registry on *Helicobacter pylori* Management (Hp-EuReg). The demographic and clinical data, diagnostic methods, treatment regimens, and prescription trends with their effectiveness were analysed by modified intention-to-treat (mITT) and per-protocol (PP) analyses. ***Results:*** Overall, 700 cases, mainly from 2 centres (98% of cases), were included, with 59% females, with a mean age of 54 ± 15 years. Treatment-naïve patients encompassed 81% of cases. Overall compliance (>90% drug intake) was reported in 99% of cases. Overall effectiveness was 87%, by both mITT and PP analyses. The triple PPI-clarithromycin-amoxicillin therapy decreased from 29% in 2013 to 0% in 2022. Conversely, both quadruple concomitant PPI-clarithromycin-amoxicillin-metronidazole and PPI-bismuth-metronidazole-tetracycline therapies were predominantly used from 2016 onwards,

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with PPI-bismuth-metronidazole-tetracycline representing 76% of all prescriptions in 2022, achieving an overall mITT effectiveness of 92% and 91%, respectively. ***Conclusion:*** In Portugal, concomitant quadruple therapy with PPI-clarithromycin-amoxicillin-metronidazole and bismuth quadruple with PPI-bismuth-metronidazole-tetracycline provided both optimal (>90%) effectiveness, in line with results of other Southern European countries.

Eficácia das Terapêuticas Empíricas de Primeira Linha em Portugal: European Registry on *Helicobacter pylori* Management (Hp-EuReg)

Palavras Chave
Endoscopia · Erradicação · Tratamento empírico

Resumo

Introdução: Portugal apresenta uma das mais elevadas taxas de cancro gástrico da Europa, tornando-se imperativo otimizar da taxa de erradicação da infeção por *H. pylori*. Pretendemos analisar os regimes terapêuticos de erradicação de *H. pylori* utilizados em Portugal, de acordo com a prática clínica. ***Métodos:*** Estudo de coorte prospetivo dos doentes portugueses diagnosticados com infeção por *H. pylori* entre maio de 2013 e dezembro de 2022, no âmbito do *European Registry on H. pylori management (Hp-EuReg)*. Os dados demográficos e clínicos, métodos de diagnóstico, esquemas terapêuticos, evolução das prescrições e eficácia foram avaliados de acordo com a análise por *intenção de tratar modificada* (mITT) e *per-protocol* (PP). ***Resultados:*** Incluídos 700 casos, maioritariamente de 2 centros (98% dos casos), com 59% doentes do género feminino, idade média de 54 ± 15 anos. Doentes naïve correspondem a 81% dos casos. Adesão global (toma >90% do fármaco prescrito) descrita em 99% dos casos. Eficácia global de 87%, nas análises mITT e PP. Observado decréscimo nas prescrições da terapêutica tripla IBP-claritromicina-amoxicilina, de 29% em 2013 para 0% em 2022. De forma contrária, as terapêuticas quádruplas concomitante PPI-claritromicina-amoxicilina-metronidazole e PPI-bismuto-metronidazole-tetraciclina foram predominantemente utilizadas a partir de 2016, com a última a representar 76% das prescrições em 2022, atingindo uma eficácia global segundo a análise por mITT de 92% e 91%, respetivamente. ***Conclusão:*** Em Portugal, as terapêuticas quádruplas concomitante PPI-claritromicina-amoxicilina-metronidazole e PPI-bismuto-metronidazole-tetraciclina, obtiveram eficácias *ótimas* (>90%), em concordância com resultados obtidos noutros países do Sul da Europa.

Introduction

Helicobacter pylori (H. pylori) is a gram-negative bacterium that infects 50% of the world's population. It is invariably associated with gastritis and may lead to severe outcomes, including peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma [1–3]. In accordance with the 2015 Kyoto consensus, Maastricht VI/Florence report states that *H. pylori* is considered an infectious disease and is now included as a specific disease entity in the new International Classification of Diseases 11th Revision (ICD11) [1, 4].

The prevalence of *H. pylori* varies across different geographical regions, with Western Europe being distinguished by one of the lowest reported occurrences [2, 3, 5]. Nevertheless, Portugal is highlighted as one of the countries facing a substantial burden, with a prevalence exceeding 60%, reaching 84% in the northern area [6, 7].

Optimal management of *H. pylori* infection is challenging due to the escalating antimicrobial bacterial resistance [8]. A Portuguese meta-analysis reveals that primary resistance rate to metronidazole (M) ranges between 10 and 34%, to clarithromycin (C) is 32%, and dual resistance to both antibiotics reaches 5% [6]. According to current guidelines, in areas with a high (>15%) C resistance rate, the recommended first-line empirical treatment consists of bismuth-containing quadruple therapy with bismuth salts (B), M, tetracycline (Tc), and a proton-pump inhibitor (PPI) (quadruple-BMTc), or non-B concomitant therapy with C, amoxicillin (A), M, and a PPI (concomitant-CAM). Standard triple therapy (triple-CA) is the recommended regimen in areas with low C resistance rate [1]; thus, it is no longer considered an acceptable treatment in the adult Portuguese population [6, 9].

H. pylori gastritis has the potential to progress to gastric cancer [10]. As Portugal exhibits some of the highest gastric cancer incidence, optimizing the *H. pylori* eradication rate becomes mandatory [11].

A recommended anti-*H. pylori* regimen is presently described as one that consistently achieves an eradication rate of at least 90% [12]. The overall effectiveness can be

classified as *excellent* (>95% success), *good* (>90% success), *borderline acceptable* (85–89% success), or *unacceptable* (<85% success) [12]. The European Registry on *Helicobacter pylori* Management (Hp-EuReg) is a platform that aggregates information on real-world *H. pylori* management across a multitude of European countries, in order to homogenize and provide a large-scale perspective on the current state of the clinical practice [13]. Our objective was to describe the management of *H. pylori* infection by evaluating the effectiveness and safety of first-line empirical treatments, in Portugal by gastroenterologists within a real clinical practice setting.

Materials and Methods

This manuscript represents the cohort of Portuguese patients within the Hp-EuReg, an international, multicentre, non-interventional registry, recording information of *H. pylori* infection management since May 2013, promoted by the European Helicobacter and Microbiota Study Group (EHMSG, www.helicobacter.org). The registry is currently receiving input from 38 European countries with the collaboration of over 300 centres. The study is still recruiting patients, without any limitation or stopping point defined; so, there is no applicable sample size. The detailed information regarding Hp-EuReg can be found in the published protocol [14].

The study was conducted according to ethical guidelines of the 1975 Declaration of Helsinki, and Hp-EuReg protocol was approved by the Ethics Local Committee of La Princesa University Hospital of Madrid (Spain), registered at ClinicalTrials.gov with code NCT02328131. The current manuscript follows the recommendation for Reporting of Observational Studies in Epidemiology (STROBE) statement [15].

Participants

Portuguese adults diagnosed with *H. pylori* infection and included in the Hp-EuReg between May 2013 and December 2022 were considered. Participants were included by gastroenterologists if submitted to any attempt of *H. pylori* treatment, without any exclusion criteria.

Information containing the patient's demographic and clinical data, diagnostic methods before and after treatment, previous eradication attempts, treatment regimen details, and its associated eradication rate and compliance was collected using an electronic case report form. Additionally, safety was assessed through the reporting of adverse events (AEs) and any required treatment interruptions due to these events. The information was registered at the Research Electronic Data Capture (REDCap) application hosted at "Asociación Española de Gastroenterología," Madrid, Spain (AEG; www.aegastro.es; accessed on January 1, 2024), a non-profit scientific and medical society of gastroenterologists whose goal is to promote research.

Data Management

After the data extraction, the database was reviewed for inconsistencies and subsequent data cleaning. The data quality review process evaluated whether the study selection criteria had been met and whether data were correctly collected, ensuring the study was conducted according to the highest scientific and ethical standards. Data discordances were resolved by querying the investigators and through group emailing. Prior to the statistical analyses, the Hp-EuReg Scientific Director ensured coherence, data quality, and scientific integrity.

Statistical Analyses

Variable Categorization and Definition

To ease the synthesis of information, our analysis focused on the 4 most frequently used treatments, defined as follows: triple-CA, sequential-CAM, concomitant-CAM, and quadruple-BMTc. Compliance with treatment was defined as taking at least 90% of the prescribed drugs.

The analysis was stratified by length of treatment (at least 7, 10, or 14 days) and PPI dose (low, standard, and high). For PPI doses, low dose was defined as 4.5–27 mg omeprazole equivalents, twice daily; and high dose was defined as 54–128 mg omeprazole equivalents, twice daily; all other doses were considered as standard [16].

Data Analysis

In order to evaluate the effectiveness of the different regimens, we performed an analysis in 3 groups of patients: an intention-to-treat (ITT) analysis, regarding data with a 6-month period follow-up and considering as treatment failures the patients lost to follow-up (i.e., the result of the confirmatory test after the eradication treatment was not available); a modified ITT (mITT) analysis, including patients that had completed the follow-up (i.e., the result of the confirmatory test after the eradication treatment was available – success or failure); regardless of whether they had complied with treatment or not, in order to closely align with everyday real clinical practice; and a per-protocol (PP) analysis included patients who had completed follow-up and were compliant (i.e., had taken ≥90% of the prescribed drugs). In

statistical analysis, continuous data were presented as the mean and standard deviation, while qualitative data were presented as the absolute relative frequencies, displayed as percentages (%) and corresponding 95% confidence intervals. Statistical analysis was performed using IBM SPSS Statistics (version 25). The selected level of statistical significance was $p < 0.05$.

Results

Overall, 700 cases were included in the Hp-EuReg in Portugal between 2013 and 2022. Patients were enrolled via outpatient clinic at five distinct medical facilities throughout Portugal, only by gastroenterologists: two centres provided 98% of cases – Instituto Português de Oncologia de Coimbra and Centro Hospitalar e Universitário do Porto, while the other cases were provided by Instituto Português de Oncologia do Porto, Centro Hospitalar de Vila Nova de Gaia e Centro Hospitalar de Tondela-Viseu.

Baseline Characteristics

There were 59% of female patients (n = 410), with a mean age of 54 ± 15 years (range 15–84), and 99% were Caucasian (n = 696). Allergy to antibiotics was registered in 4.4% (n = 31), most of them to penicillin 4% (n = 28). The main indications for *H. pylori* eradication were dyspeptic symptoms (47%), duodenal ulcer (3.7%), gastric ulcer (3.7%), and other causes (39%) that included anaemia and atrophic gastritis.

H. pylori diagnosis, before eradication treatment, was mainly made through invasive strategies: histology 90% (n = 627), culture 2.3% (n = 16), and rapid urease test 0.3% (n = 2); the most used non-invasive test was ^{13}C urea breath test 4.9% (n = 34). The eradication confirmatory test was performed in 93% of the cases (n = 649), with 7.3% of the patients lost to follow-up (n = 51). The diagnostic methods after eradication were also analysed, with ^{13}C urea breath test in 64% (n = 448), ^{14}C urea breath test in 23% (n = 159), and histology in 5.9% (n = 41) being the most frequently used confirmatory test choices.

Prescriptions

Regarding the therapeutic regimens, the most frequently prescribed schemes were the quadruple therapy, including the concomitant-CAM in 32% (n = 226) and the quadruple-BMTc in 31% (n = 215), followed by triple-CA in 27% (n = 186). Other unfrequently used prescriptions such as concomitant-CAM for 10 days or quadruple-BMTc for 14 days had no more than 17 cases and were not eligible for statistical analysis.

Table 1. Therapeutic regimens prescribed as first-line treatment

Treatment regimen	Patients, *N* (%)
Concomitant-CAM	180 (32)
Quadruple-BMTc	152 (27)
Triple-CA	114 (20)
Sequential-CAM	50 (9)
Triple-CM	6 (1)
Triple-AM	5 (1)
Sequential-CATc	4 (1)
Quadruple-CML	4 (1)
Triple-CL	3 (1)
Triple-AL	3 (1)
Sequential-ATcL	1 (0.2)
Sequential-A	1 (0.2)
Quadruple-CATc	1 (0.2)

A, amoxicillin; B, bismuth; C, clarithromycin; L, levofloxacin; M, metronidazole; Tc, tetracycline.

The prescription strategy of the PPIs was also analysed, with esomeprazole being the leading choice 37% (n = 257), followed by pantoprazole 29% (n = 199), rabeprazole 20% (n = 141), omeprazole 13% (n = 88), and lansoprazole 2% (n = 12). In 98% of the cases, the PPIs were prescribed twice a day and once a day in 2%. The low PPI dosage (i.e., 20 mg omeprazole equivalent twice daily) was the most used PPI prescription in 40% (n = 276) cases.

First-Line Therapy Effectiveness

From the 700 studied cases, 81% (n = 564) received a first-line empirical treatment, and out of 16 different therapeutic regimens, 13 were prescribed as first-line therapy, reported in Table 1. Patients who underwent first-line eradication therapy were mainly prescribed with concomitant-CAM (n = 180, 32%), quadruple-BMTc (n = 152, 27%), triple-CA (n = 114, 20%), and sequential-CAM (n = 50, 9%).

The mITT and PP effectiveness of each first-line treatment regimen are presented in Table 2. After confirming eradication with a validated diagnostic test, the overall effectiveness of *H. pylori* first-line eradication therapy was 87% by both mITT and PP. Concomitant-CAM (92%) and quadruple-BMTc (91%) obtained optimal (>90%) effectiveness.

Table 2. PP and mITT effectiveness in first-line empirical treatment

Treatment regimen	PP, *n/N* (%)	95% CI	mITT, *n/N* (%)	95% CI
Concomitant-CAM	91.7% (165/180)	87.6%–95.7%	91.7% (165/180)	87.6%–95.7%
Quadruple-BMTc	91.4% (139/152)	87.0%–95.9%	91.4% (139/152)	87.0%–95.9%
Triple-CA	81.3% (91/112)	74.0%–88.5%	80.7% (92/114)	74.0%–88.5%
Sequential-CAM + M	84% (42/50)	73.8%–94.2%	84% (42/50)	73.8%–94.2%

A, amoxicillin; B, bismuth; C, clarithromycin; M, metronidazole; Tc, tetracycline; PP, per-protocol; mITT, modified intention-to-treat; 95% CI, 95% confidence interval.

An eradication confirmatory test was performed in 649 patients, and the remaining were incomplete or lost to follow-up. The duration of treatment and the PPI dosage used in the most frequently prescribed first-line regimens are recorded in Table 3. There were no significant differences in effectiveness rates between the low-dose PPI versus standard/high-dose PPI, regardless of the length of the treatment, within quadruple-BMTc, concomitant-CAM, triple-CA, and sequential-CAM. Regarding the treatment duration, the majority (n = 320, 57%) of patients were treated with 14-day concomitant-CAM and 10-day quadruple-BMTc. Only 2 patients received a 7-day duration regimen. According to the analysis of all treated patients, those who received first-line treatments were predominantly treated with low-dose PPIs (n = 214, 38%).

Safety and Compliance

Two patients (0.4%) prescribed with triple-CA therapy discontinued the medication due to AEs (diarrhoea, nausea, and vomits). AEs were reported by 11% (n = 59), with dysgeusia (5%), nausea (4%), and diarrhoea (3%) being the most common. Among those who completed the eradication test, treatment compliance was achieved by 99% of the patients (643/649).

Rescue Therapy

From the 700 studied cases, 13% (n = 93) received a second-line empirical treatment, 5% (n = 36) received a third line, and 1% (n = 7) were prescribed with a fourth therapy line. Patients who underwent second-line treatment were mainly prescribed with triple therapy with amoxicillin and levofloxacin (n = 30, 32%), quadruple-BMTc (n = 25, 27%), and concomitant-CAM (n = 18, 19%). The mITT effectiveness of each of these second-line treatments was 60% (18/30), 91% (19/21), and 93% (14/15), respectively.

Temporal Trend Analysis

When evaluating the trends of *H. pylori* eradication success from 2013 to 2022 (Fig. 1), it was observed that the effectiveness, according to mITT, fluctuated along the years of the study. Figure 2 represents the evolution of the prescriptions between 2013 and 2022. The triple-CA therapy exhibited a declining trend after reaching its peak in 2019, with 0% prescriptions by 2022. A similar pattern was observed with sequential-CAM. Conversely, quadruple therapies, concomitant-CAM, and quadruple-BMTc were predominantly used since 2016, being the two most used regiments since 2017, with quadruple-BMTc being the top prescribed regimen since 2019 and reaching 76% of all prescriptions in 2022.

The trends in the prescription of PPI dosage are illustrated in Figure 3, reflecting a tendency towards an increase in the use of higher PPI doses and a decrease in standard and low doses between 2013 and 2022. In 2022, the rates for high versus standard versus low PPI doses were 48% versus 38% versus 14%, respectively. Also, trends regarding the length of prescription changed from mainly 7 days until the year 2016, where 10- and 14-day therapies became the preferred options. In 2022, these 2 lengths represented 86% of all prescribed regimens.

Discussion

In Portugal, the overall first-line treatment effectiveness in our cohort was reported as 87%, placing it within the category of *borderline acceptability*, according to the mITT analysis [12]. Similar results were obtained in the PP analysis, which can be attributed to the high rate of treatment compliance, due to the similar sample size. The absence of specific Portuguese guidelines that consider the local pattern of antibiotic resistance makes the treatment of *H. pylori* infection a persistent challenge.

Table 3. Treatment duration and PPI dosage in first-line empirical therapy

Treatment regimen	PPI dose, *N* (%)						Treatment duration, *N* (%)					
	low	95% CI	standard	95% CI	high	95% CI	7 days	95% CI	10 days	95% CI	14 days	95% CI
Concomitant-CAM	65 (33.3%)	26.7%–39.9%	60 (30.8%)	24.3%–37.3%	70 (35.9%)	29.2%–42.6%	0	–	17 (10%)	6.2%–13.8%	150 (90%)	86.2%–93.8%
Quadruple-BMTc	71 (41.8%)	34.4%–49.2%	39 (22.9%)	16.6%–29.3%	60 (35.3%)	28.1%–42.5%	0	–	170 (99.4%)	98.1%–100%	1 (0.6%)	0%–3.3%
Triple-CA	40 (34.4%)	26.5%–43.5%	55 (47.4%)	38.6%–56.4%	21 (18.1%)	12.2%–26.1%	2 (4.8%)	0%–13.1%	5 (12%)	3.2%–22.8%	35 (83.3%)	74.7%–91.9%
Sequential-CAM	38 (73.1%)	66.5%–79.7%	8 (15.3%)	5.6%–25.0%	6 (11.5%)	2.5%–21.3%	0	–	51 (98.1%)	95.1%–100%	1 (1.9%)	0%–9.4%

A, amoxicillin; B, bismuth; C, clarithromycin; M, metronidazole; Tc, tetracycline; PPI, proton-pump inhibitor (low dose: 4.5–27 mg omeprazole equivalents, twice daily; high dose: 54–128 mg omeprazole equivalents, twice daily; all other doses were considered as standard); 95% CI, 95% confidence interval.

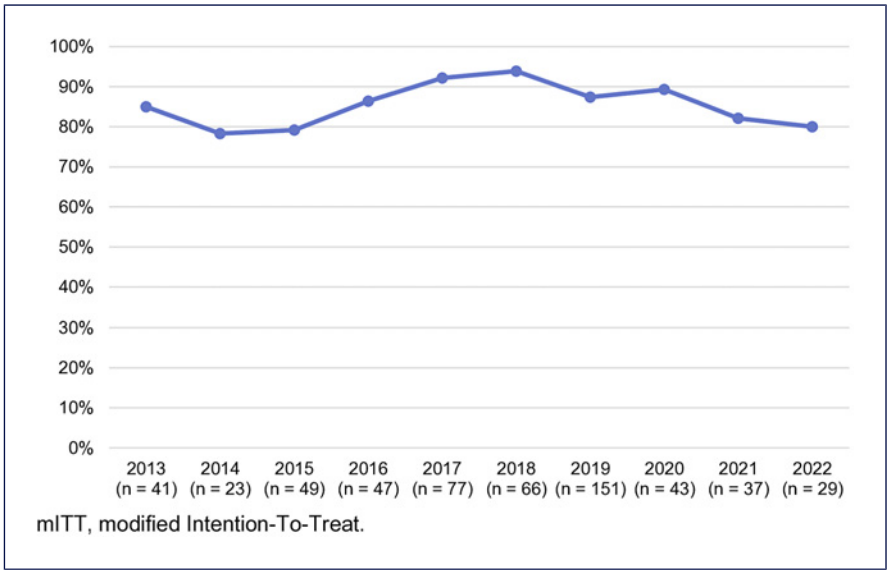

Fig. 1. Trends in *H. pylori* eradication effectiveness by mITT analysis during the years 2013–2022. mITT, modified intention-to-treat.

Due to the unavailability of an optimal therapeutic regimen, there was a gradual evolution of prescriptions, involving mainly quadruple regimens, longer prescription durations, and higher PPI doses over time [17, 18]. In fact, in our study, it was observed that quadruple therapies achieved eradication rates of 91%, according to the mITT analysis, classified as *good*.

A study conducted by Nyssen et al. [13] with data from the Hp-EuReg, which included 21,533 treatment-naïve patients across 27 European countries distributed in five geographical regions, assessed the prescriptions and effectiveness trends of first-line empirical treatment over a 5-year period. The study reported that only quadruple therapies (with a minimum duration of 10 days) achieved nearly 90% eradication rates, with the quadruple-BMTc treatment proving highest results. Similarly, a Spanish Hp-EuReg sub-study concluded that the highest eradication rates were obtained with the same quadruple-BMTc (95%), the quadruple-BCA (91%), and the concomitant-CAM (90%), particularly when treatment was optimized (during 14 days and concomitantly with standard PPI doses, i.e., 40 mg omeprazole equivalent twice a day) [18]. Furthermore, in an Italian Hp-EuReg cohort study, it was observed that for the 10-day

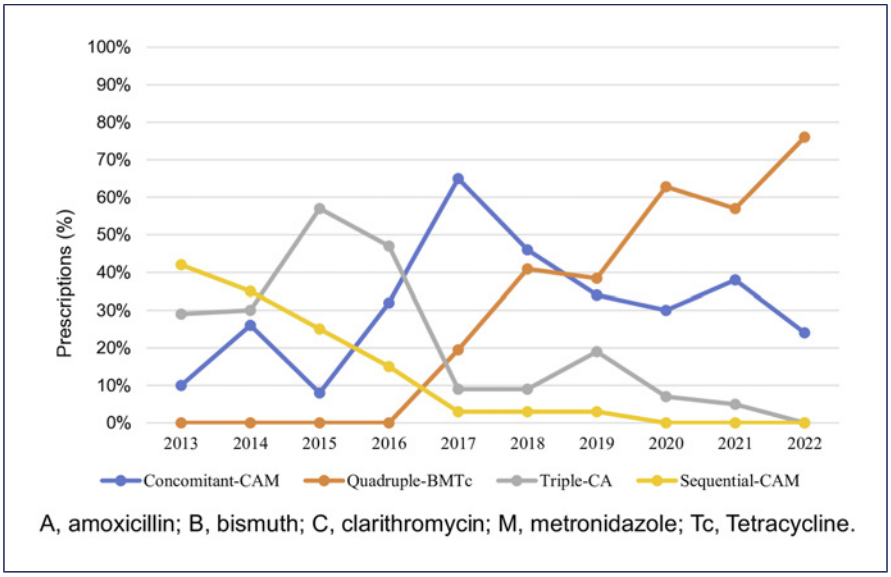

Fig. 2. Trends in the prescription of the four most frequently used first-line empirical treatments during the years 2013–2022. A, amoxicillin; B, bismuth; C, clarithromycin; L, levofloxacin; M, metronidazole; Tc, tetracycline.

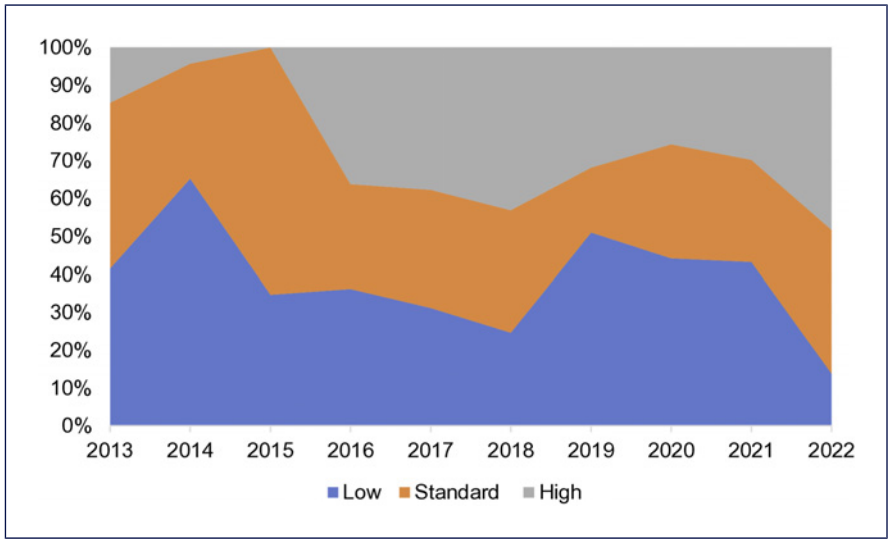

Fig. 3. Trends in the first-line empirical prescription of the dose of PPIs during the years 2013–2022. Low dose: 4.5–27 mg omeprazole equivalents, twice daily; high dose: 54–128 mg omeprazole equivalents, twice daily; all other doses were considered as standard.

therapies, only quadruple-BMTc, concomitant-CAM, sequential-CAM, and 14-day concomitant-CAM reached an eradication rate ≥90% [19]. Our results in Portugal were in line with the aforementioned findings.

The use of quadruple-BMTc regimen represents the first-line option therapy in regions with high C resistance (>15%), given there is no resistance of *H. pylori* to B and minimal, if any, to Tc, which could eventually lead to the withdrawal of culture and susceptibility testing [20–22]. B as isolated medication is unavailable in Portugal, leading to the use of quadruple-BMTc therapy formulation as single capsule (marketed as Pylera®). This capsule is prescribed during 10 days. It has a 3-in-one capsule strategy (encompassing B, M, and Tc within one single capsule), intended to decrease the pill burden and enhance compliance [22]. This therapeutic option became commercially available in Portugal in March 2016, a detail that is evident in Figure 2 [20]. In our setting, should this capsule be locally unavailable, the recommended regimen is concomitant-CAM, which also achieved satisfactory results in our study. In line with our results, the finding was of a randomized trial reporting that, in fully compliant patients, the efficacy of concomitant-CAM therapy was 100% in Italy and 94.5% in Spain, with common mild side effects [22]. Another randomized controlled study compared the efficacy of 10-

day concomitant-CAM versus 10-day quadruple-BMTc versus 14-day triple-CA as first-line treatments: while the 10-day quadruple-BMTc demonstrated superior efficacy (90%), the 10-day concomitant-CAM and 14-day triple-CA had lower eradication rates (86% and 84%, respectively) [23]. These findings suggest that a 10-day duration for concomitant-CAM therapy may be insufficient, and the recommendation to extend the duration to 14 days, as suggested in the Maastricht VI/Florence consensus report, should be considered [23]. In our cohort, the majority of concomitant-CAM was administered for a duration of 14 days, aligning with the current guidelines' recommendations [1].

Triple-CA therapy remains the most used treatment option for the eradication of *H. pylori* infection in clinical practice in Europe [17, 24]. Nevertheless, only a limited number of regions remain below the threshold defined as low (<15%) C resistance, and a significant reduction in the proportion of eradication has been observed when this therapy is used [1, 9, 24]. It is possible to observe this change in our cohort, characterized by a decreasing trend in triple-CA therapy prescriptions during the studied time span. Despite the change in guidelines, which initially suggested that triple-CA therapy could be administered for 7 to 10–14 days, the recommendation transitioned in 2017 to a 14-day duration for this regimen [25, 26]. In our study, although seven (17%) patients underwent triple therapy either for 7 days or 10 days, the majority (83%) received the prescribed 14-day duration.

Sequential-CAM therapy demonstrates inadequate eradication rates in regions with dual resistance to M and C, a frequent scenario in Portugal [6, 22, 27]. However, it is important to highlight that, regarding sequential therapy, the sample size of patients prescribed with the referred therapy was inferior and the mITT analysis showed an effectiveness rate below 90%, which is in line with the current literature. Sequential-CAM therapy can be considered a complex regimen due to the required medication change midway through the treatment period; however, this did not impact compliance in our cohort [1]. Since it has shown inferior effectiveness compared to concomitant-CAM therapy, it is currently not recommended as first-line treatment in current European Consensus Guidelines [1, 24, 28]. Our results met the Maastricht VI/Florence consensus report, showing a decrease in the prescription of the aforementioned regimen [26].

When evaluating the prescription of the eradication schemes, we observed a marked heterogeneity, with 13 different therapeutic regimens prescribed as first-line treatments. The variability likely derives from the absence of Portuguese consensus guidelines during the study period. To ease the understanding of our data, our analysis focused on the four most prescribed therapeutical regimens covering 95% of the data cohort conferring sufficient representativeness of the sample. In 2019, there was an increase in the variety of prescriptions used, and we are unaware why. Also, although an association between the increased use of both concomitant-CAM and quadruple-BMTc treatment and a decreased *H. pylori* eradication treatment effectiveness was observed, with rates failing from 92% to 80%, we could not find an underlying cause for this association.

PPIs play a crucial role in *H. pylori* eradication treatment, as the effectiveness of antibiotics is optimized at higher gastric pH levels [16]. There is evidence suggesting that high-dose PPIs enhance eradication rates compared to standard doses, particularly in regions with high bacterial resistance [29]. A recent meta-analysis revealed that esomeprazole and rabeprazole exhibited superior eradication rates [30]. Latest VI Maastricht consensus guidelines state that high-dose PPI twice daily enhances the efficacy of triple therapy; however, in our cohort, low-dose PPI was twice the most frequent prescriptions as compared to higher PPI doses [1, 26]. We are unaware of the cause of non-adherence with the guidelines.

It is agreed that the best approach to have an effective *H. pylori* eradication is to succeed on the first-line treatment, to avoid retreating and retesting [31]. Since compliance is one of the strongest independent factors associated with effectiveness, it is of utmost importance to achieve it [13, 22]. In our cohort, treatment compliance was reported in 99% of the patients, which was excellent. Another important factor together with compliance is reducing the impact of bacterial antibiotic resistance, an envisioned goal for an optimized therapeutical approach. However, currently there is no sufficient evidence to advocate the generalized use of susceptibility-guided therapy for *H. pylori* treatment in real clinical practice, given continuous monitoring of the current resistance prevalence would be essential as well as challenging, to assess which treatment would be more effectively tailored to meet specific cure needs [32, 33].

Among the limitations of this study, the fact that the Hp-EuReg is not a randomized, controlled trial might affect the interpretation of the results. And so, in current observational study, there is no information regarding the rationale behind the physicians' prescriptions. Another drawback is that we had few centres participating, most of the cases coming mainly from two centres, and all being tertiary departments; so, only gastroenterologists recruited patients

for inclusion, without representation of primary care facilities. During the data analysis, the presence of collinearity within our cohort prevented us from conducting a multivariate analysis. The univariate analysis revealed no significant differences in eradication rates between the various treatment groups. As a result, our findings are based on the descriptive data from our cohort.

The strengths of our study include its prospective and real clinical practice nature. Our study evaluated the patterns of therapeutic regimens prescribed over 10 years of clinical practice, covering a wide range of years, which offers the scientific community a comprehensive perspective on the evolution of local anti-*H. pylori* eradication strategies. This provides the Portuguese literature with significant insights into *H. pylori* treatment management, with robust conclusions that can be readily applied in clinical practice.

To conclude, the Portuguese Hp-EuReg sub-study found that concomitant-CAM and quadruple-BMTc therapies achieved optimal (>90%) effectiveness, aligning with those therapies achieving optimal effectiveness in other Southern European countries, also characterized by similar high antibiotic resistance prevalence patterns. There was a verified discontinuation of triple-CA therapy, with preferred eradication regimens evolving to mainly quadruple regimens, longer treatment durations, and higher PPI doses over time, which was in accordance with the international guidelines. Periodic studies like this are valuable for gathering information on adherence to guidelines and assessing the effectiveness of the current therapeutical regimens implemented in Portugal as well as identifying the room for improvement in our setting. Looking ahead, future research should focus on tailoring therapies based on local data to enhance treatment outcomes and reduce the emergence of antibiotic resistance.

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Statement of Ethics

The study was conducted according to ethical guidelines of the 1975 Declaration of Helsinki, and Hp-EuReg protocol was approved by the Ethics Local Committee of La Princesa University Hospital of Madrid (Spain), which acted as a reference Institutional Review Board (December 20, 2012), was classified by the Spanish Drug and Health Product Agency, and registered at ClinicalTrials.gov with code NCT02328131. This is a non-interventional study, and the registry does not include any data that might compromise confidentiality beyond age and gender and does not involve any modification to daily clinical practice, so the patients were not requested to sign an informed consent. All analysed data were kept confidential, and the investigators have ensured the anonymity of the patients included during data analysis and publication.

Conflict of Interest Statement

Dr. Gisbert has served as a speaker, a consultant, and advisory member for or has received research funding from Mayoly, Allergan, DiaSorin, Biocodex, Juvisé, and Richen. Dr. Nyssen has received research funding from Mayoly, Allergan, DiaSorin, Biocodex, Juvisé, and Richen. The remaining authors declare no conflicts of interest.

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Author Contributions

Maria Inês Viegas and Miguel Areia coordinated current study; analysed, synthetized, and interpreted the data; wrote the first draft; and approved the submitted manuscript. Luís Elvas, Ricardo Marcos-Pinto, Henrique Fernandes-Mendes, Susana Alves, Daniel Brito, Sandra Saraiva, and Ana Teresa Cadime collected data, critically reviewed the manuscript's drafts, and approved the final submitted manuscript. Anna Cano-Català and Pablo Parra performed the monitoring and quality check of the data, and approved the final manuscript. Olga P. Nyssen, Hp-EuReg Scientific Director, planned and coordinated current study, performed the data extraction, supervised the monitoring and the data quality check, performed the analysis, assisted with interpretation and synthesis of data, critically reviewed the manuscript's drafts, and approved the final submitted manuscript. Anna Cano-Català, Pablo Parra, Leticia Moreira, Olga P. Nyssen, Francis Mégraud, Colm O'Morain, and Javier P. Gisbert are all members of the Hp-EuReg Scientific Committee, critically reviewed the manuscript's

drafts, and approved the final submitted manuscript. Javier P. Gisbert, Principal Investigator of the registry, directed the project, obtained funding, designed the protocol, planned and coordinated current study, recruited patients, critically reviewed the manuscript drafts, and approved the final submitted manuscript.

Data Availability Statement

All data analysed during this study are included in the article. Further enquiries can be directed to the corresponding author, OPN (Scientific Director of the Hp-EuReg) or the JPG (PI of the Hp-EuReg).

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